

We claim:

1. A recombinant Ca^{2+} dependent monoclonal antibody immunoreactive with an epitope in the activation peptide region of the heavy chain of Protein C defined by E D Q V D P R L I D G K (Sequence ID No. 1) in combination with calcium, where the antibody inhibits Protein C activation by thrombin-thrombomodulin.

2. The antibody of claim 1 comprising amino acid sequence selected from the group consisting of:

MGR LSSS FLL LIAPAYVLSQ VTLKESGPGI LQPSQTLTLT CSLSGFSLRT
SGMGVGWIRQ PSGKGLEWLA HIWDDDKRY NPVLKSRLII SKDTSRKQVF
LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (Sequence
ID No. 10); MDFQVQIFSF LLISASVIMS RGQIILTQSP
AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLAGVP
SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR
(Sequence ID No. 12); Q VTLKESGPGI LQPSQTLTLT
CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWDDDKRY NPVLKSRLII
SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS
(amino acids 20-139 of Sequence ID No. 10) and
QIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY
GTSNLAGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG
GGTKLEIKR (amino acids 23-129 of Sequence ID No. 12).

3. The antibody of claim 1 containing human amino acid sequence.

4. The antibody of claim 1 encoded in part by a nucleotide sequence selected from the group consisting of ATGGGCAGGC TTTCTTCTTC ATTCTTGCTA
CTGATTGCCC CTGCATATGT CCTGTCCCAG GTTACTCTGA AAGAGTCTGG
CCCTGGGATA TTGCAGCCCT CCGAGACCCT CACTCTGACT TGTCTCTCT
CTGGGTTTTC ACTGAGGACT TCTGGTATGG GTGTAGGCTG GATTCGTCAG
CCTTCAGGGA AGGGTCTGGA GTGGCTGGCA CACATTTGGT GGGATGATGA
CAAGCGCTAT AACCCAGTCC TGAAGAGCCG ACTGATAATC TCCAAGGATA

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CCTCCAGGAA ACAGGTATTC CTCAAGATCG CCAGTGTGGA CACTGCAGAT
 ACTGCCACAT ACTACTGTGT TCGAATGATG GATGATTACG ACGCTATGGA
 CTACTGGGGT CAAGGAACCT CAGTCACCGT CTCCTCT (Sequence ID
 No. 9); CAG GTTACTCTGA AAGAGTCTGG CCCTGGGATA
 TTGCAGCCCT CCCAGACCCT CACTCTGACT TGTCTCTCT CTGGGTTTTC
 ACTGAGGACT TCTGGTATGG GTGTAGGCTG GATTCGTCAG CCTTCAGGGA
 AGGGTCTGGA GTGGCTGGCA CACATTTGGT GGGATGATGA CAAGCGCTAT
 AACCCAGTCC TGAAGAGCCG ACTGATAATC TCCAAGGATA CCTCCAGGAA
 ACAGGTATTC CTCAAGATCG CCAGTGTGGA CACTGCAGAT ACTGCCACAT
 ACTACTGTGT TCGAATGATG GATGATTACG ACGCTATGGA CTACTGGGGT
 CAAGGAACCT CAGTCACCGT CTCCTCT (nucleotides 58 to 417
 of Sequence ID No. 9); ATGGATTTTC AGGTGCAGAT
 TTTCAGCTTC CTGCTAATCA GTGCCTCAGT CATAATGTCC AGAGGACAAA
 TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT GGGGGAGGAG
 ATCACCTAA CCTGCAGTGC CACTTCGAGT GTAACCTACG TCCACTGGTA
 CCAGCAGAAG TCAGGCACTT CTCCCAAACCT CTTGATTTAT GGGACATCCA
 ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA GTGGCAGTGG
 GTCTGGGACC TTTTATTCTC TCACAGTCAG CAGTGTGGAG GCTGAAGATG
 CTGCCGATTA TTAAGTCCAT CAGTGGGAATA GTTATCCGCA CACGTTCCGA
 GGGGGGACCA AGCTGGAAAT AAAACGG (Sequence ID No. 11); - HPC-4 VL
 CAAA TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT
 GGGGGAGGAG ATCACCTAA CCTGCAGTGC CACTTCGAGT GTAACCTACG
 TCCACTGGTA CCAGCAGAAG TCAGGCACTT CTCCCAAACCT CTTGATTTAT
 GGGACATCCA ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA
 GTGGCAGTGG GTCTGGGACC TTTTATTCTC TCACAGTCAG CAGTGTGGAG
 GCTGAAGATG CTGCCGATTA TTAAGTCCAT CAGTGGGAATA GTTATCCGCA
 CACGTTCCGA GGGGGGACCA AGCTGGAAAT AAAACGG (nucleotides
 67 to 387 of Sequence ID No. 11); and degenerate
 sequences thereof.

5. The antibody of claim 1 further
 comprising a pharmaceutically acceptable carrier for
 administration to a patient.

6. The antibody of claim 5 further
 comprising a cytokine or an inducer of cytokine
 expression in a dosage effective in combination with

the antibody to coagulate microvasculature in tumors but not in the absence of the antibody.

7. The antibody of claim 1 having a detectable label bound to the antibody.

8. The antibody of claim 1 immobilized to a substrate, wherein the immobilized antibody is suitable for purification of protein C from a biological fluid.

9. A method for treating a disorder by inhibition of protein C anticoagulant comprising administering to a patient in need of treatment thereof an effective amount of a recombinant Ca^{2+} dependent monoclonal antibody immunoreactive with an epitope in the activation peptide region of the heavy chain of Protein C defined by E D Q Y D P R L I D G K (Sequence ID No. 1) in combination with calcium, where the antibody inhibits Protein C activation by thrombin-thrombomodulin.

10. The method of claim 9 wherein the antibody comprises amino acid sequence selected from the group consisting of:

MGR LSSS FLL LIAPAYVLSQ VTLKESGPGI LQPSQTLTLT CSLSGFSLRT
SGMGVGWIRQ PSGKGLEWLA HIWDDDKRY NPVLKSRLII SKDTSRKQVF
LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (Sequence
ID No. 10); MDFQVQIFSF LLISASVIMS RGQIILTQSP
AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP
SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR
(Sequence ID No. 12); Q VTLKESGPGI LQPSQTLTLT
CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWDDDKRY NPVLKSRLII
SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS
(amino acids 20-139 of Sequence ID No. 10) and
QIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY
GTSNLASGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG
GGTKLEIKR (amino acids 23-129 of Sequence ID No. 12).

11. The method of claim 9 wherein the antibody contains human amino acid sequence.

12. The method of claim 9 wherein the antibody is encoded in part by a nucleotide sequence selected from the group consisting of ATGGGCAGGC

TTTCTTCTTC ATTCTTGCTA CTGATTGCCC CTGCATATGT CCTGTCCCAG
 GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT CCCAGACCCT
 CACTCTGACT TGTTCTCTCT CTGGGTTTTT ACTGAGGACT TCTGGTATGG
 GTGTAGGCTG GATTCGTCAG CCTTCAGGGA AGGCTCTGGA GTGGCTGGCA
 CACATTTGGT GGGATGATGA CAAGCGCTAT AACCCAGTCC TGAAGAGCCG
 ACTGATAATC TCCAAGGATA CCTCCAGGAA ACAGGTATTC CTCAAGATCG
 CCAGTGTGGA CACTGCAGAT ACTGCCACAT ACTACTGTGT TCGAATGATG
 GATGATTACG ACGCTATGGA CTACTGGGGT CAAGGAACCT CAGTCACCGT
 CTCCTCT (Sequence ID No. 9); CAG GTTACTCTGA AAGAGTCTGG
 CCCTGGGATA TTGCAGCCCT CCCAGACCCT CACTCTGACT TGTTCTCTCT
 CTGGGTTTTT ACTGAGGACT TCTGGTATGG GTGTAGGCTG GATTCGTCAG
 CCTTCAGGGA AGGGTCTGGA GTGGCTGGCA CACATTTGGT GGGATGATGA
 CAAGCGCTAT AACCCAGTCC TGAAGAGCCG ACTGATAATC TCCAAGGATA
 CCTCCAGGAA ACAGGTATTC CTCAAGATCG CCAGTGTGGA CACTGCAGAT
 ACTGCCACAT ACTACTGTGT TCGAATGATG GATGATTACG ACGCTATGGA
 CTACTGGGGT CAAGGAACCT CAGTCACCGT CTCCTCT (nucleotides
 58 to 417 of Sequence ID No. 9); ATGGATTTTC AGGTGCAGAT
 TTTCAGCTTC CTGCTAATCA GTGCCTCAGT CATAATGTCC AGAGGACAAA
 TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT GGGGAGGAG
 ATCACCCTAA CCTGCAGTGC CACTTCGAGT GTAACCTACG TCCACTGGTA
 CCAGCAGAAG TCAGGCACTT CTCCCAAACCT CTTGATTTAT GGGACATCCA
 ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA GTGGCAGTGG
 GTCTGGGACC TTTTATTCTC TCACAGTCAG CAGTGTGGAG GCTGAAGATG
 CTGCCGATTA TTAAGTCCAT CAGTGGAATA GTTATCCGCA CACGTTCCGA
 GGGGGGACCA AGCTGGAAAT AAAACGG (Sequence ID No. 11);
 CAAA TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT
 GGGGGAGGAG ATCACCCTAA CCTGCAGTGC CACTTCGAGT GTAACCTACG
 TCCACTGGTA CCAGCAGAAG TCAGGCACTT CTCCCAAACCT CTTGATTTAT
 GGGACATCCA ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA
 GTGGCAGTGG GTCTGGGACC TTTTATTCTC TCACAGTCAG CAGTGTGGAG

GCTGAAGATG CTGCCGATTA TTACTGCCAT CAGTGGAATA GTTATCCGCA
CACGTTCCGA GGGGGGACCA AGCTGGAAAT AAAACGG (nucleotides
67 to 387 of Sequence ID No. 11); and degenerate
sequences thereof.

13. The method of claim 9 further
comprising administering with the antibody a cytokine
or other chemotherapeutic agent in an amount effective
to coagulate the microvasculature of a tumor.

14. A method of making a recombinant Ca^{2+}
dependent monoclonal antibody immunoreactive with an
epitope in the activation peptide region of the heavy
chain of Protein C defined by E D Q V D P R L I D G K
(Sequence ID No. 1) in combination with calcium, where
the antibody inhibits Protein C activation by
thrombin-thrombomodulin, by expressing nucleotide
sequence encoding the antibody.

15. The method of claim 14 wherein the
antibody comprises amino acid sequence selected from
the group consisting of:
MGRLLSSSFL LIAPAYVLSQ VTLKESGPGI LQPSQTLTLT CSLSGFSLRT
SGMGVGWIRQ PSGKGLEWLA HIWDDDKRY NPVLKSRLII SKDTSRKQVF
LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (Sequence
ID No. 10); MDFQVQIFSF LLISASVIMS RGQIILTQSP
AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLAGVP
SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR
(Sequence ID No. 12); Q VTLKESGPGI LQPSQTLTLT
CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWDDDKRY NPVLKSRLII
SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS
(amino acids 20-139 of Sequence ID No. 10) and
QIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY
GTSNLAGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG
GGTKLEIKR (amino acids 23-129 of Sequence ID No. 12).

16. The method of claim 14 wherein the
antibody is encoded in part by a nucleotide sequence

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selected from the group consisting of ATGGGCAGGC
 TTTCTTCTTC ATTCTTGCTA CTGATTGCCC CTGCATATGT CCTGTCCCAG
 GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT CCCAGACCCT
 CACTCTGACT TGTTCTCTCT CTGGGTTTTT ACTGAGGACT TCTGGTATGG
 GTGTAGGCTG GATTCGTCAG CCTTCAGGGA AGGGTCTGGA GTGGCTGGCA
 CACATTTGGT GGGATGATGA CAAGCGCTAT AACCCAGTCC TGAAGAGCCG
 ACTGATAATC TCCAAGGATA CCTCCAGGAA ACAGGTATTC CTCAAGATCG
 CCAGTGTGGA CACTGCAGAT ACTGCCACAT ACTACTGTGT TCGAATGATG
 GATGATTACG ACGCTATGGA CTACTGGGGT CAAGGAACCT CAGTCACCGT
 CTCCTCT (Sequence ID No. 9); CAG GTTACTCTGA AAGAGTCTGG
 CCCTGGGATA TTGCAGCCCT CCCAGACCCT CACTCTGACT TGTTCTCTCT
 CTGGGTTTTT ACTGAGGACT TCTGGTATGG GTGTAGGCTG GATTCGTCAG
 CCTTCAGGGA AGGGTCTGGA GTGGCTGGCA CACATTTGGT GGGATGATGA
 CAAGCGCTAT AACCCAGTCC TGAAGAGCCG ACTGATAATC TCCAAGGATA
 CCTCCAGGAA ACAGGTATTC CTCAAGATCG CCAGTGTGGA CACTGCAGAT
 ACTGCCACAT ACTACTGTGT TCGAATGATG GATGATTACG ACGCTATGGA
 CTACTGGGGT CAAGGAACCT CAGTCACCGT CTCCTCT (nucleotides
 58 to 417 of Sequence ID No. 9); ATGGATTTTC AGGTGCAGAT
 TTTCAGCTTC CTGCTAATCA GTGCCTCAGT CATAATGTCC AGAGGACAAA
 TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT GGGGGAGGAG
 ATCACCCTAA CCTGCAGTGC CACTTCGAGT GTAACCTACG TCCACTGGTA
 CCAGCAGAAG TCAGGCACTT CTCCCAAACCT CTTGATTTAT GGGACATCCA
 ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA GTGGCAGTGG
 GTCTGGGACC TTTTATTCTC TCACAGTCAG CAGTGTGGAG GCTGAAGATG
 CTGCCGATTA TTA CTGCCAT CAGTGAATA GTTATCCGCA CACGTTCCGA
 GGGGGGACCA AGCTGGAAAT AAAACGG (Sequence ID No. 11);
 CAAA TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT
 GGGGGAGGAG ATCACCCTAA CCTGCAGTGC CACTTCGAGT GTAACCTACG
 TCCACTGGTA CCAGCAGAAG TCAGGCACTT CTCCCAAACCT CTTGATTTAT
 GGGACATCCA ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA
 GTGGCAGTGG GTCTGGGACC TTTTATTCTC TCACAGTCAG CAGTGTGGAG
 GCTGAAGATG CTGCCGATTA TTA CTGCCAT CAGTGAATA GTTATCCGCA
 CACGTTCCGA GGGGGGACCA AGCTGGAAAT AAAACGG (nucleotides
 67 to 387 of Sequence ID No. 11); and degenerate
 sequences thereof.

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17. The method of claim 14 further comprising inserting human sequence into the antibody in place of animal sequence.

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18. The method of claim 14 further comprising binding detectable label to the antibody.

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19. The method of claim 14 further comprising immobilizing the antibody to a substrate, wherein the immobilized antibody is suitable for purification of protein C from a biological fluid.

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